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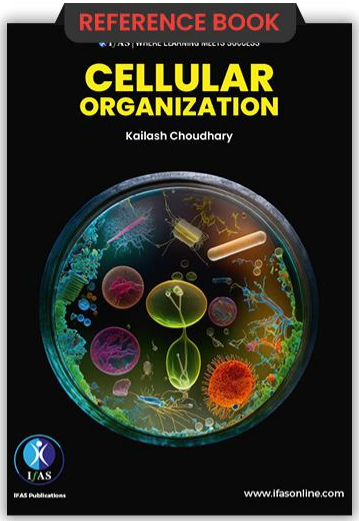
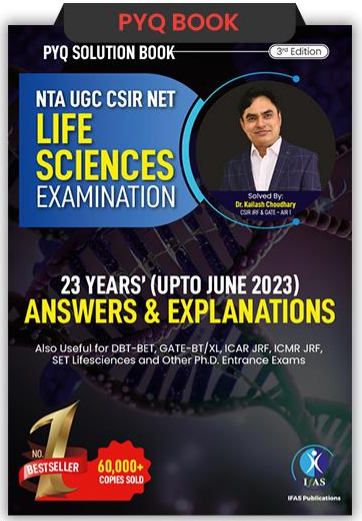
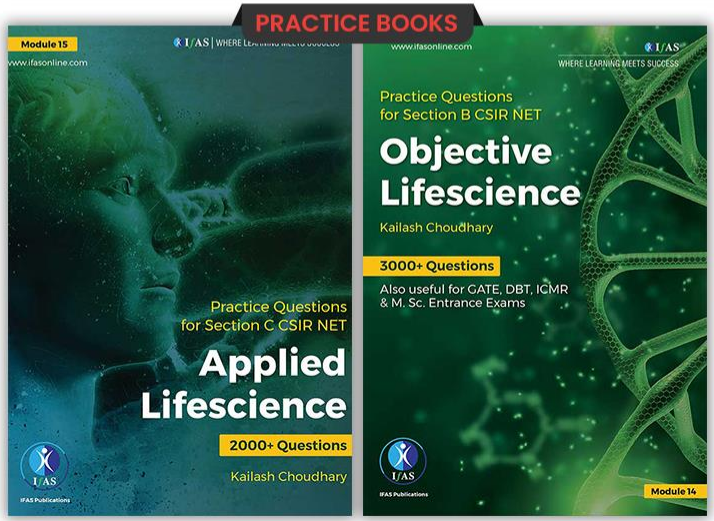
CSIR NET – Life Science

Unit 2: Cellular Organization

L15 Regulation of Cell Cycle







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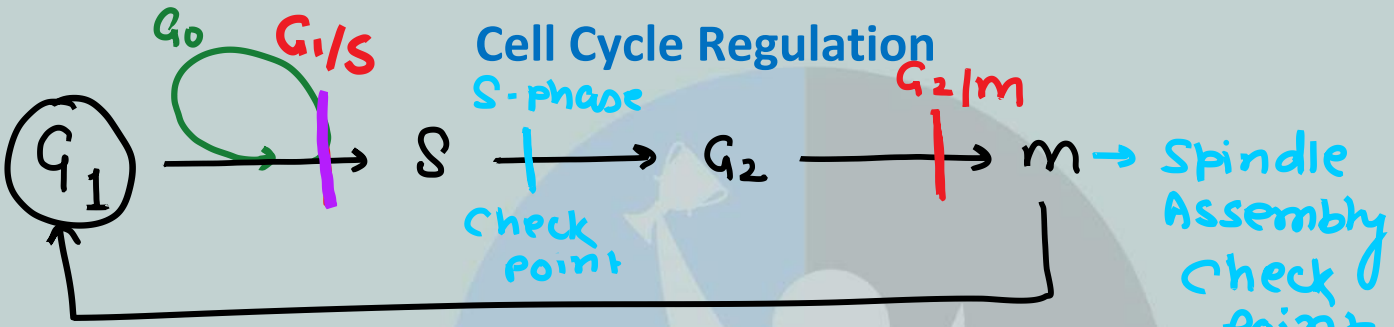
Points to be covered in this Lecture

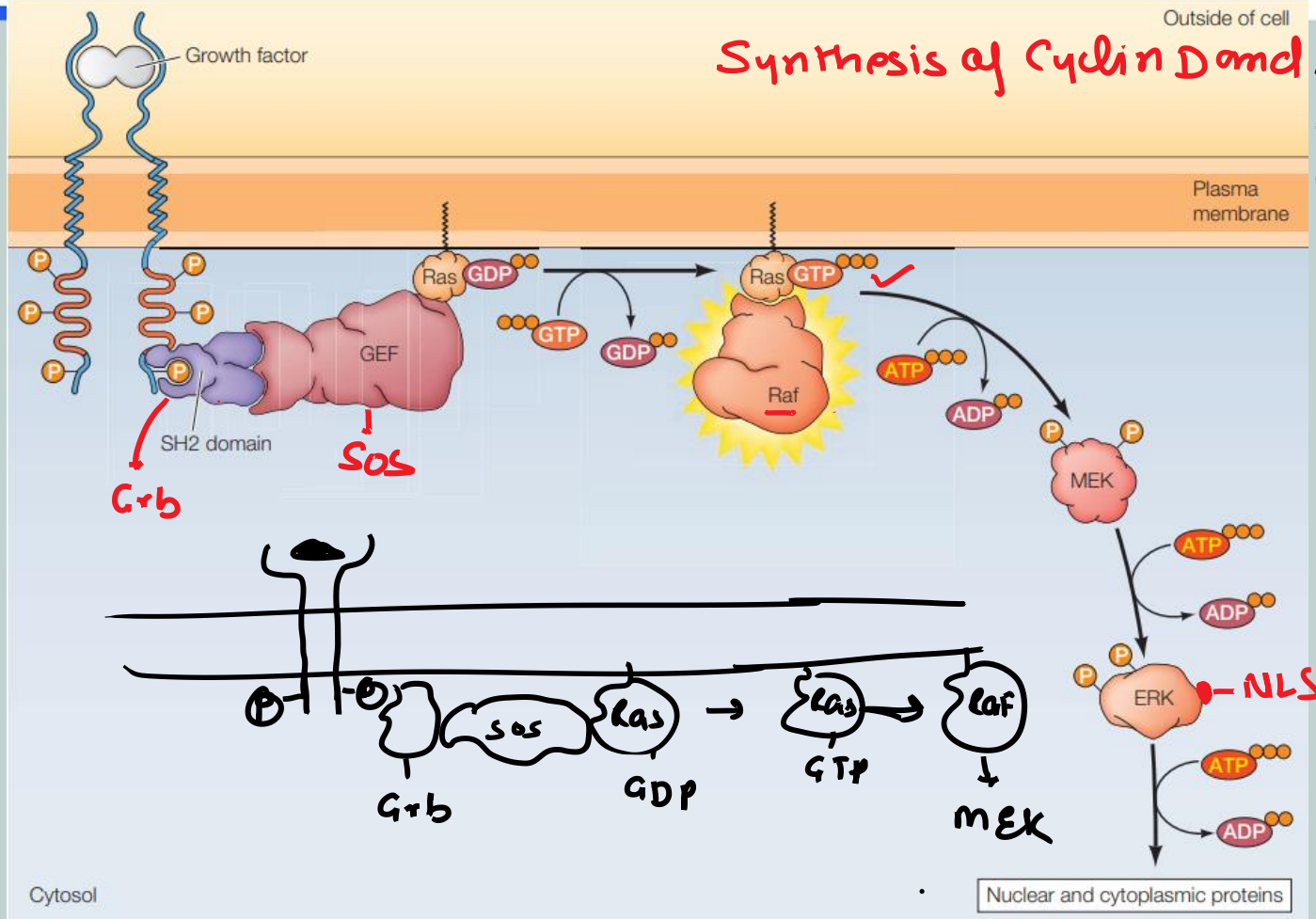
- Regulation of Cell Cycle
- Cell cycle check points
- DNA damage and cell cycle arrest
- Replication initiation licensing G2/M transition



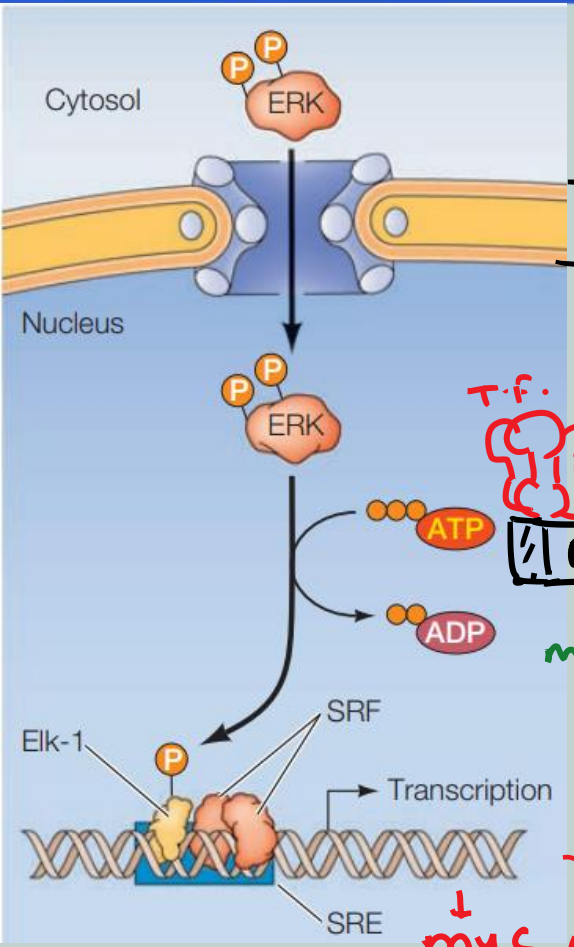
G_1 Phase

CDK 4,6
+
Cyclin D → Synthesis of Cyclin D for G_1 Stage

Inactive, Active



Activation of Cyclin E and CDK complex for G1/S checkpoints



T.F.

P | Cyclin D

mRNA

myc, fos, Jun

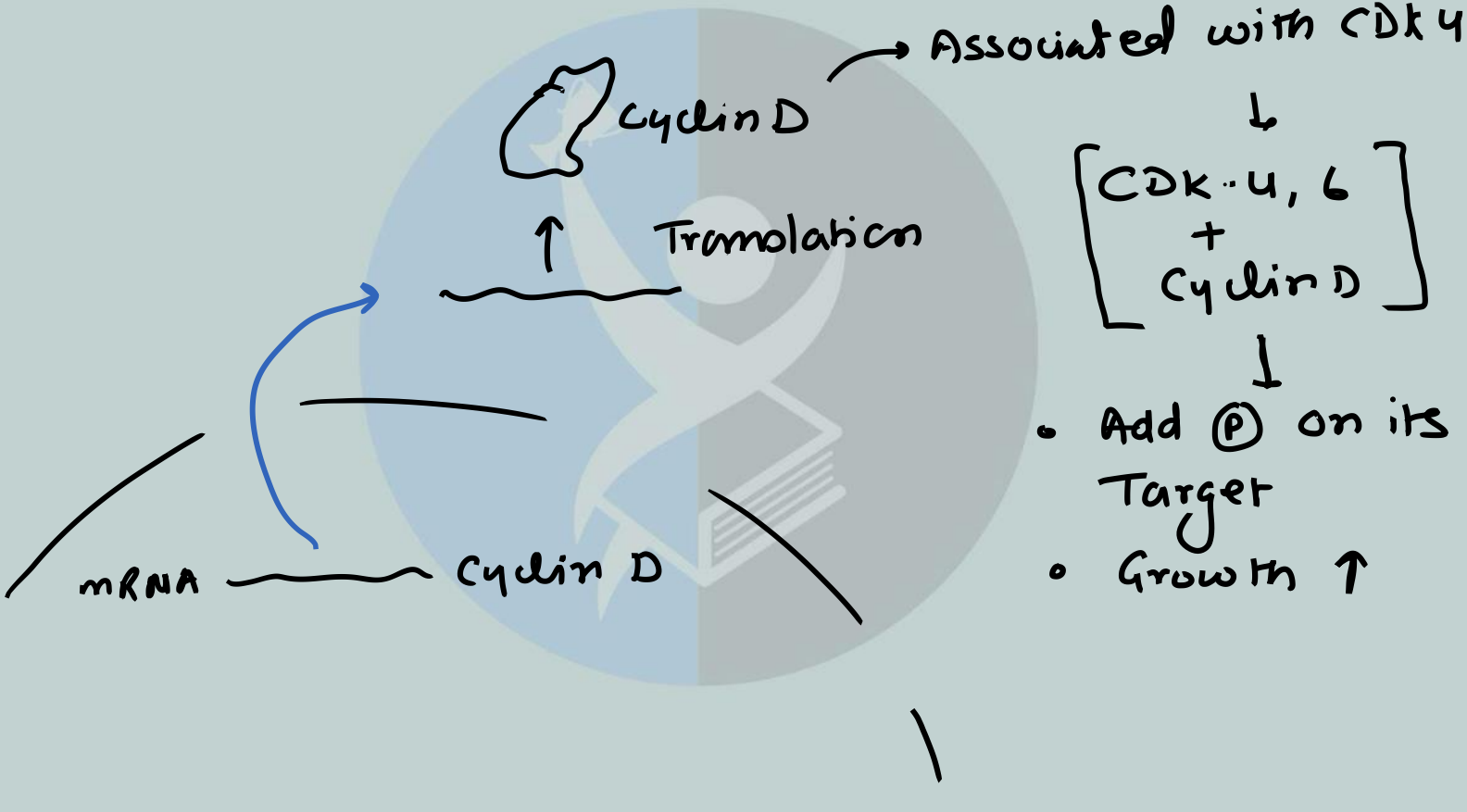
(T.F)

Translation

myc

fos

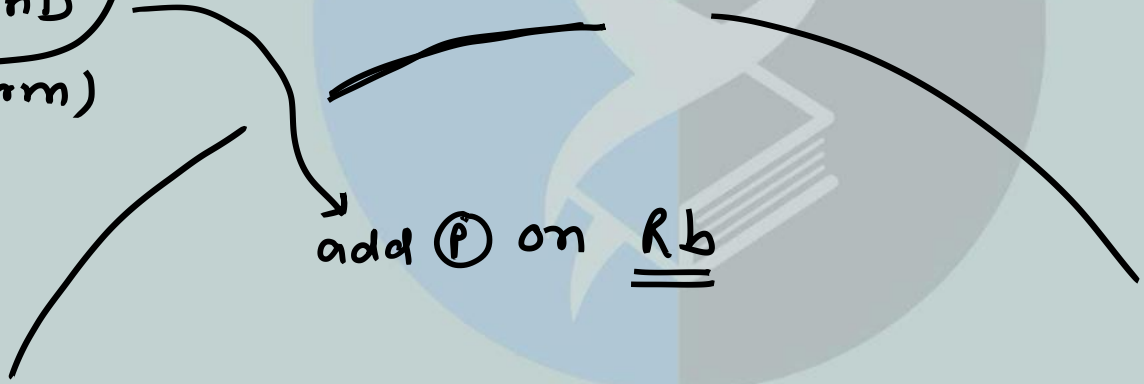
Jun

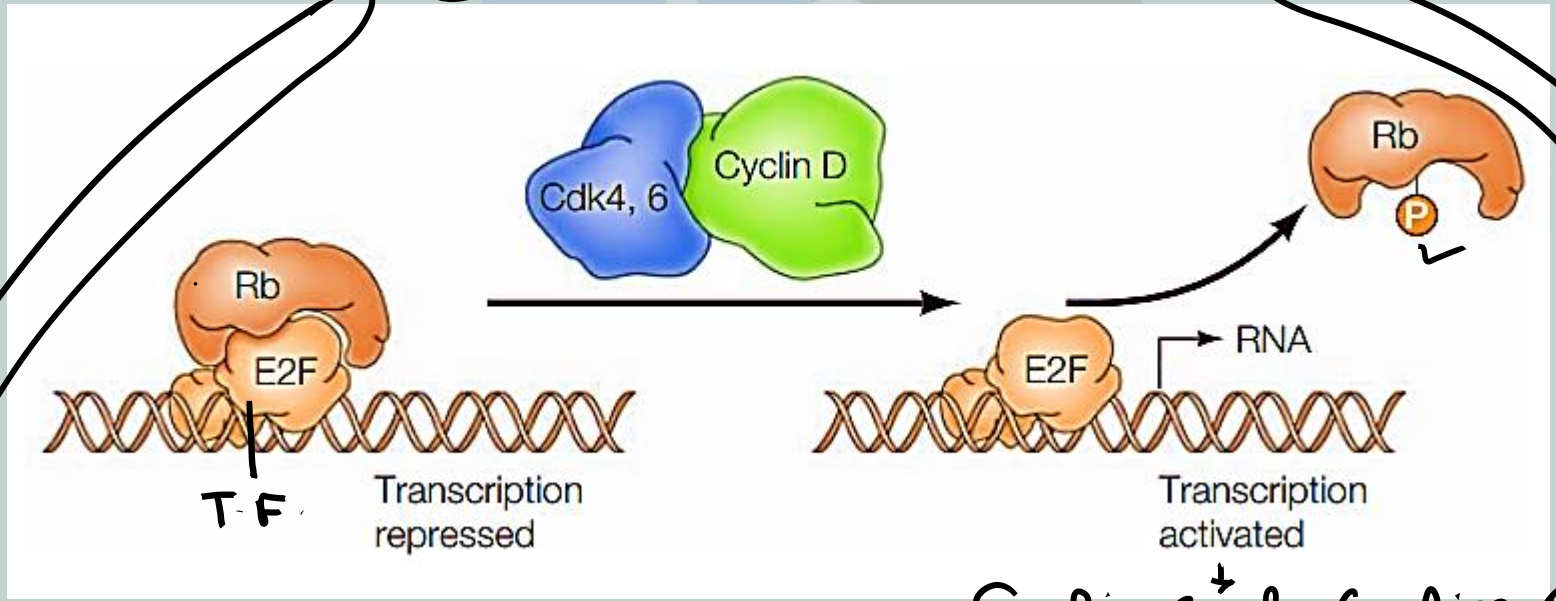

Cyclin D
Associated with CDK 4,6
Translation
[CDK-4, 6 + Cyclin D]
mRNA
Cyclin D
• Add (P) on its Target
• Growth ↑

G_1 phase ⟶ G_1/S check Point

- CDK 2 – Already +nt
- Cyclin E is required

CDK 4 + CyclinD (Isoform)





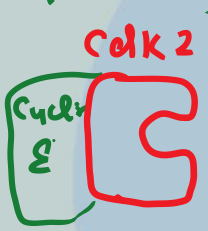
Cyclin E & Cyclin A

G_1 ⟶ G_1/S → S phase

[CdK4,6 + Cyclin D]

[CdK-2 + Cyclin E]

[CdK-2 + Cyclin A]



Sic-1

↓

Achive ✓

↓

Inactive [due to Sic-1]

G_1/S Check Point

Checking For DNA Damage

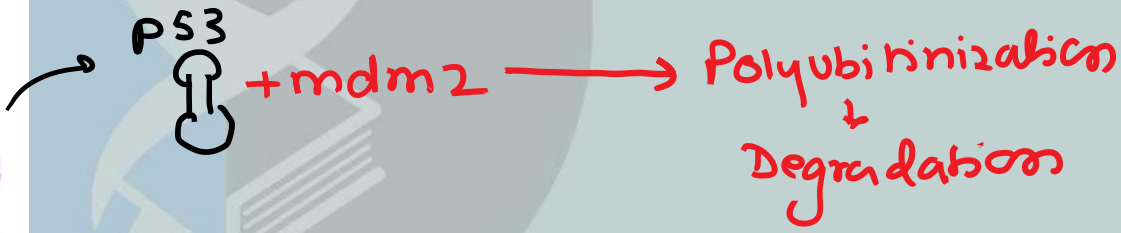
Undamaged DNA

$(ATM)_2$ inactive

ATR not signaling

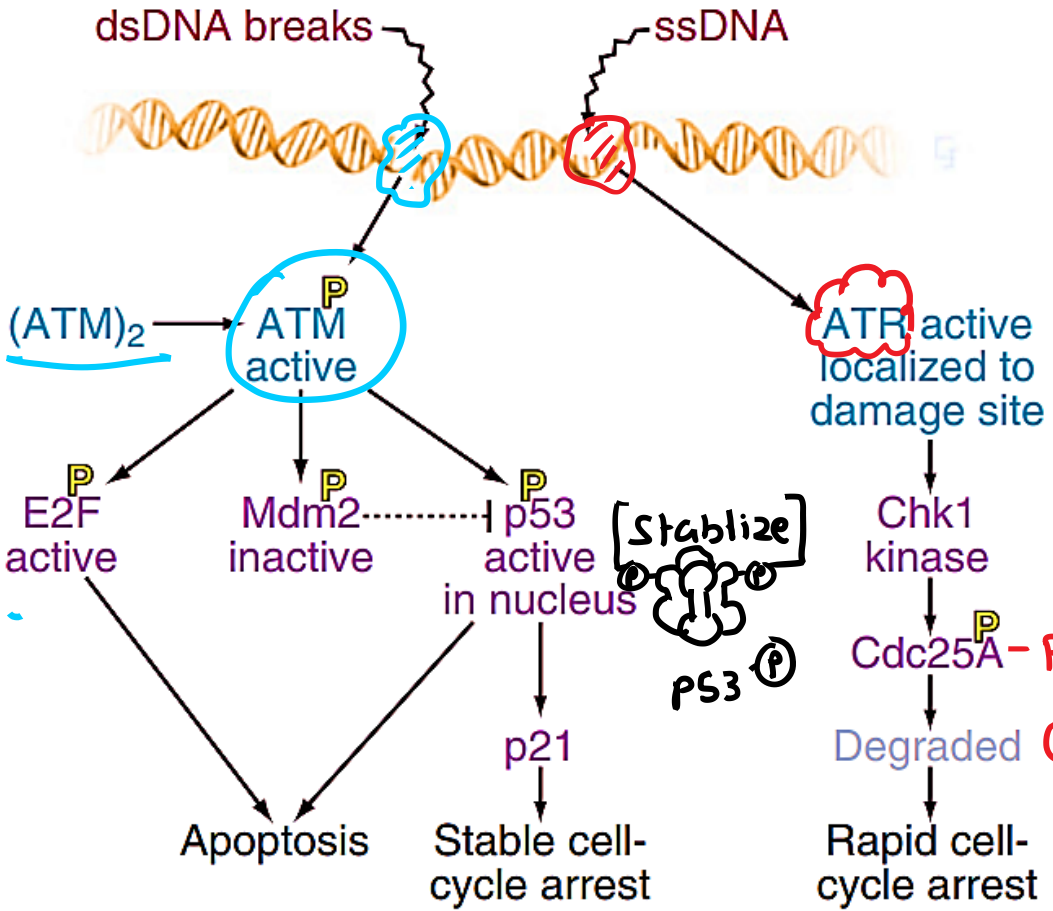
E2F drives expression of cell cycle genes

p53 present in low amounts in cytoplasm



Normal cell-cycle progression

THE G1/S CHECKPOINT AND DNA DAMAGE RESPONSE.



Stablize

p53 - active

act as T.F.

p16 [INK-4] ⊥ cdk4 ↓ G_1

p21 [INK2] ⊥ cdk2 ↓ S phase

✓ Puma ⊥ x Bcl2 ⊥ ✓ Bak, Bax ↓ ✓ Apoptosis

Cdc25A - Phosphatase

Degraded (Polyubiquitinization)

- **Proto-oncogene/growth promoting gene**

RTK, RAS, RAF, MEK, ERK, ELK, Cyclin, CDK, E2F, Cdc25, Phosphatase, Myc, fos, Jun

↓

If gain of function

↓

Oncogene

↓

cancer,

↓

single copy mutation is sufficient

Tumor suppressor gene

- INK4, INK2,
- CIP, KIP, sic1, RB,
- P53

If mutated (loss of function)

↓

double copy mutation is required

↓

Cancer

Exception - P53

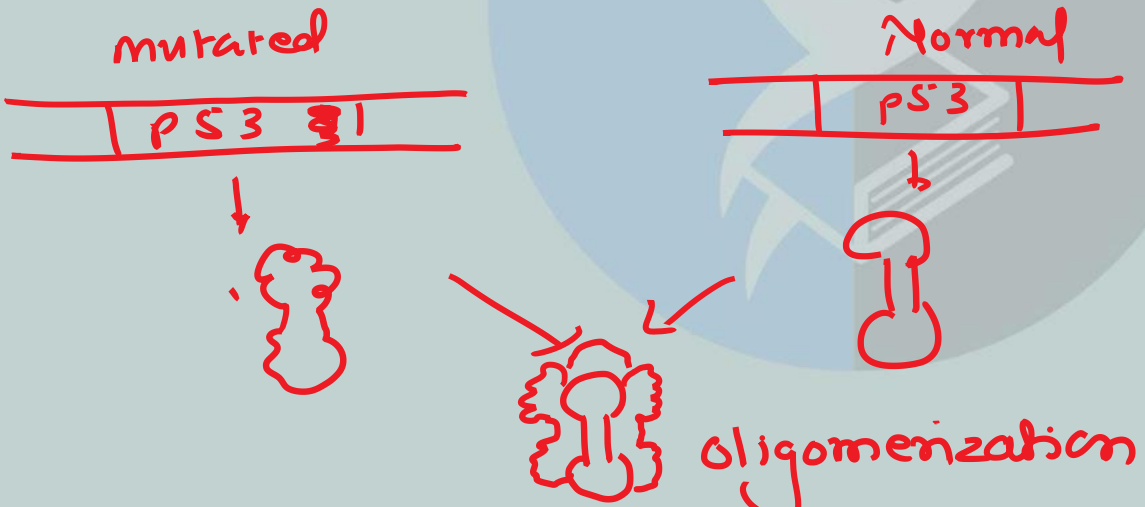
P53 is example of negative dominant effect

↓

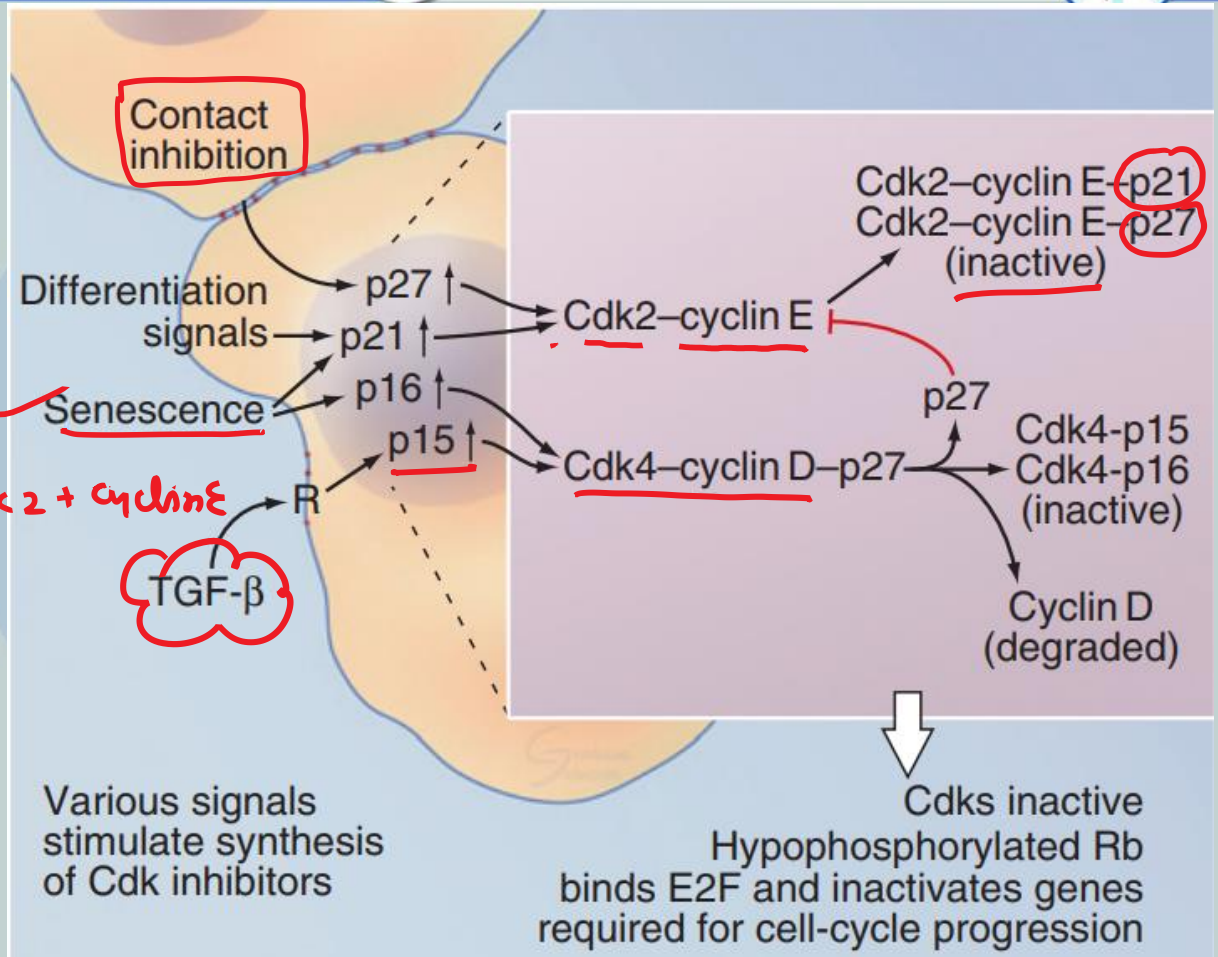
Single copy mutation,

↓

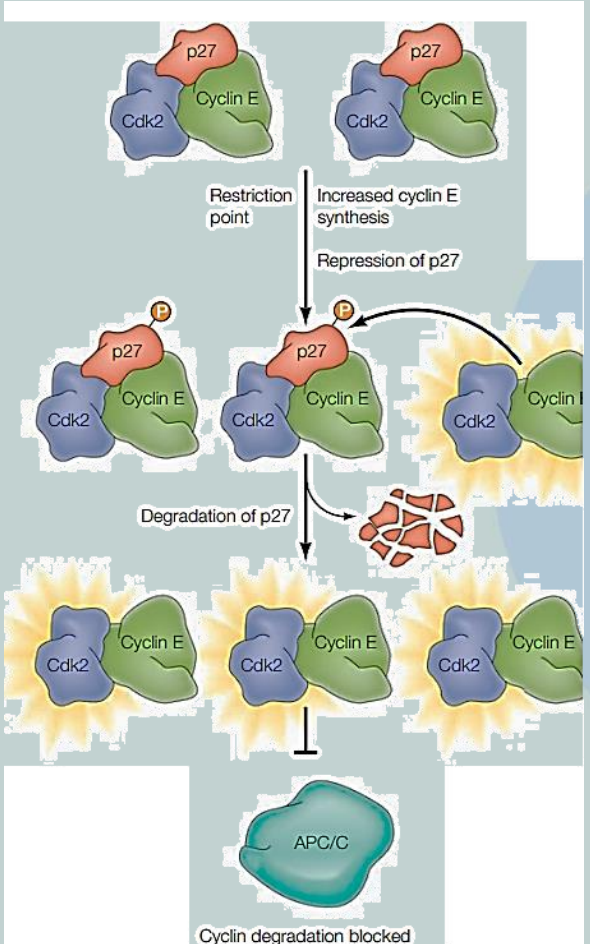
loss of function is sufficient to cause cancer



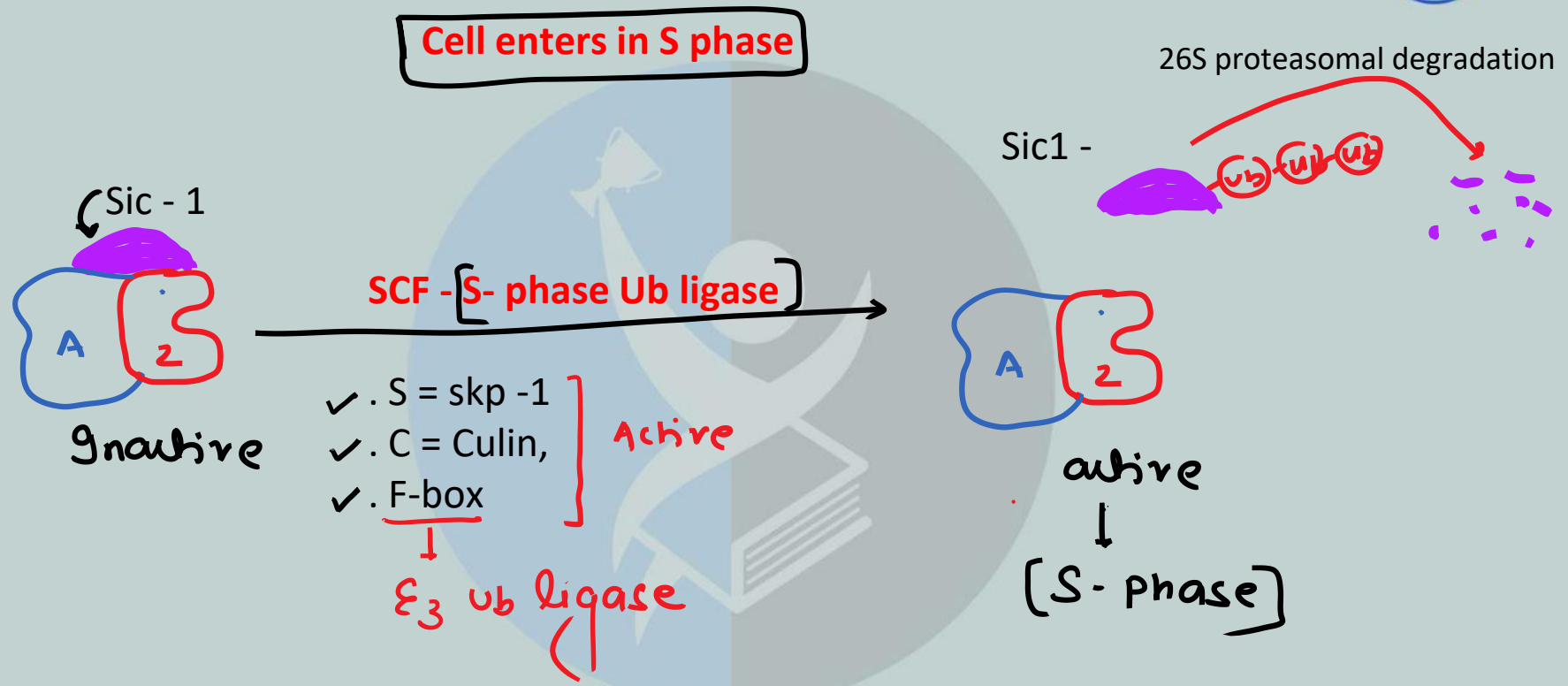
HOW EXTERNAL STIMULI ACT ON CDK INHIBITORS TO CAUSE CELLS TO ENTER A NONDIVIDING G0 STATE

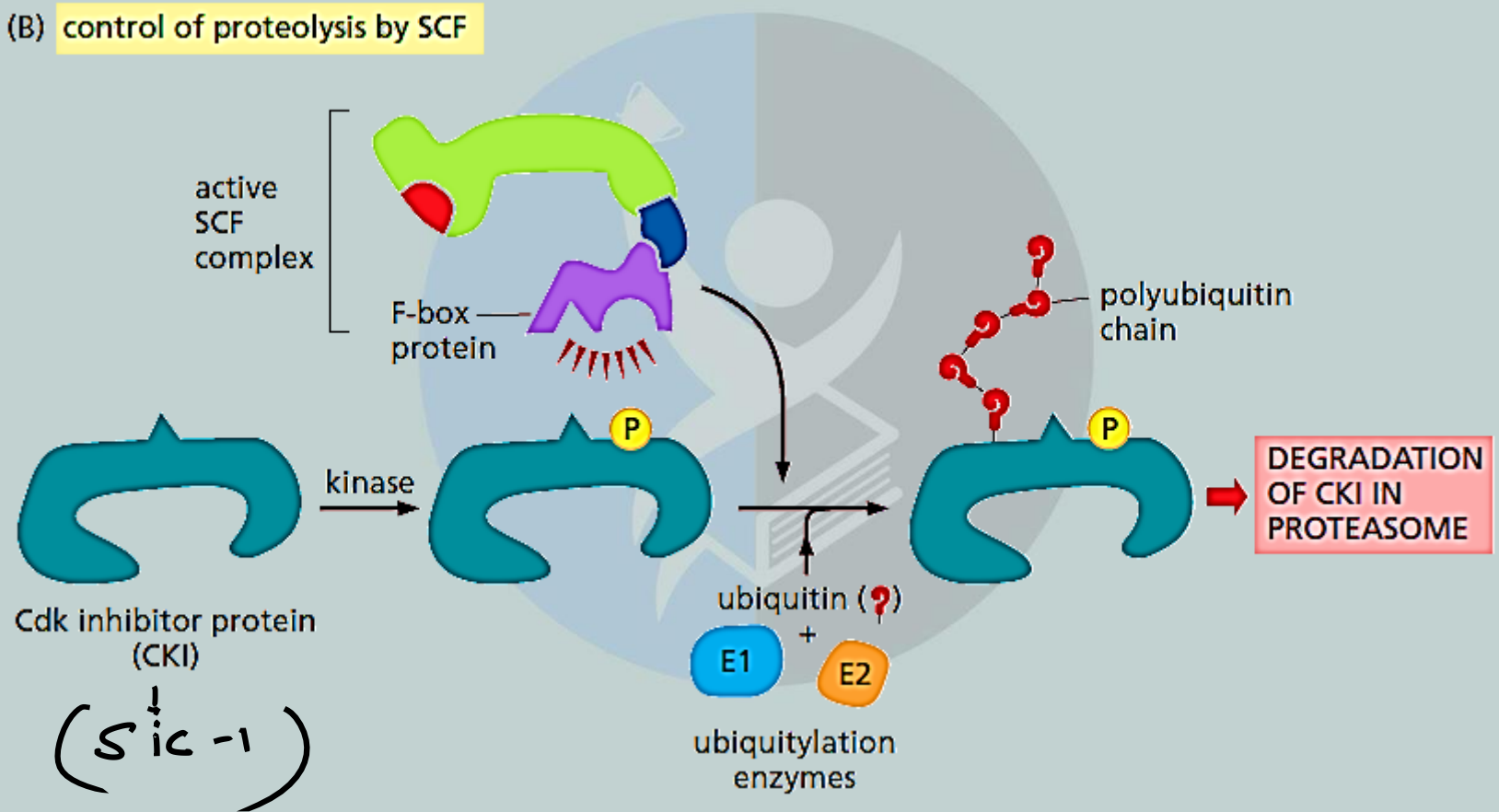


contact inhibition → p27 ⊣ cdk2 + cyclin E
→ p21 ⊣



E2F induces cyclin E, and Cdk2/ cyclin E complexes inactivate the APC/C ubiquitin ligase and drive progression through the restriction point and into S phase


Cell enters in S phase
26S proteasomal degradation
Sic1 -
Ub Ub Ub
Sic - 1
A
Z
SCF - [S- phase Ub ligase]
✓. S = skp -1
✓. C = Culin,
✓. F-box
Active
E3 ub ligase
Inactive
A
Z
active
[S- phase]


(B) control of proteolysis by SCF
active SCF complex
F-box protein
polyubiquitin chain
P
kinase
P
DEGRADATION OF CKI IN PROTEASOME
Cdk inhibitor protein (CKI)
(Sic-1)
ubiquitin (?)
+
E1
E2
ubiquitylation enzymes

- S- Phase Start

S phase CDK cyclin active

S phase DDK active (DBF dependent kinase)

Add phosphate on its target

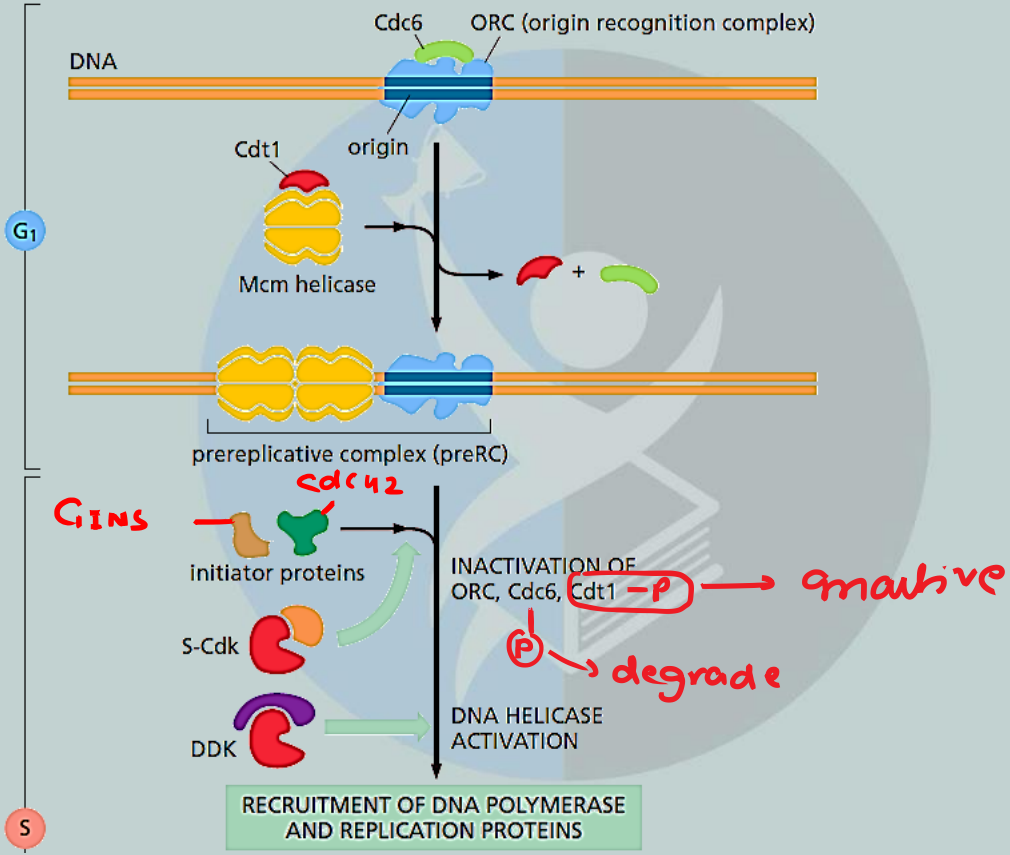
- S phase CDK add phosphate on Cdc6 (P) → Degrade
- DDK add phosphate on cdt1 (P) → Inactive

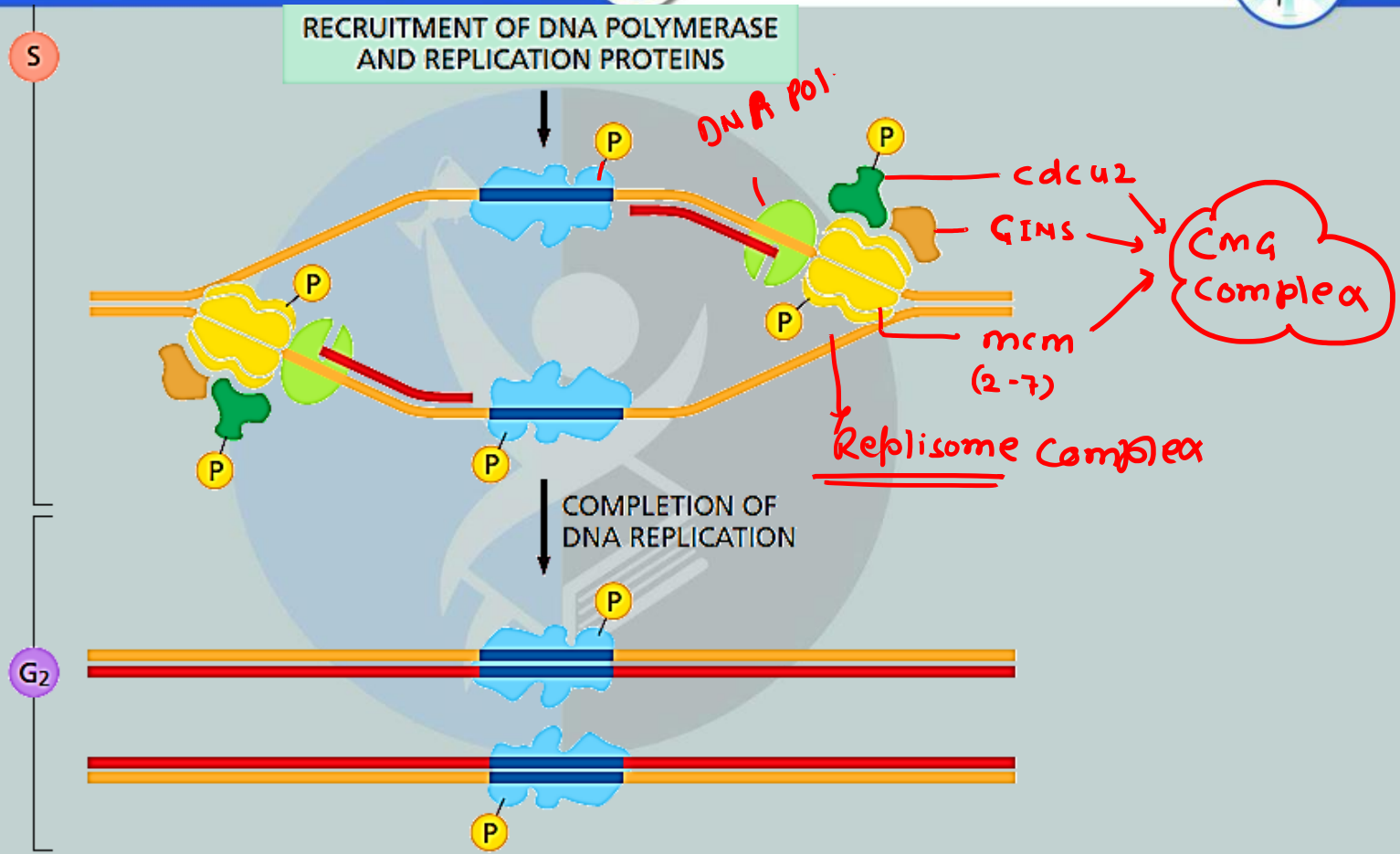
Pre-replication [Early G1 phase]

Cdc6 and Cdt 1 known as licensing factor complex G1 phase S phase DDK, CDK

↓

• or Helicase loader


Cdc6
ORC (origin recognition complex)
DNA
origin
Cdt1
G1
Mcm helicase
+
prereplicative complex (preRC)
cdc42
GINS
initiator proteins
INACTIVATION OF
ORC, Cdc6, Cdt1 –P
inactive
S-Cdk
P
degrade
DDK
DNA HELICASE
ACTIVATION
S
RECRUITMENT OF DNA POLYMERASE
AND REPLICATION PROTEINS


S
RECRUITMENT OF DNA POLYMERASE AND REPLICATION PROTEINS
DNA Pol
P
cdc42
GINS
Cmg Complex
mcm (2-7)
Replisome complex
COMPLETION OF DNA REPLICATION
G2

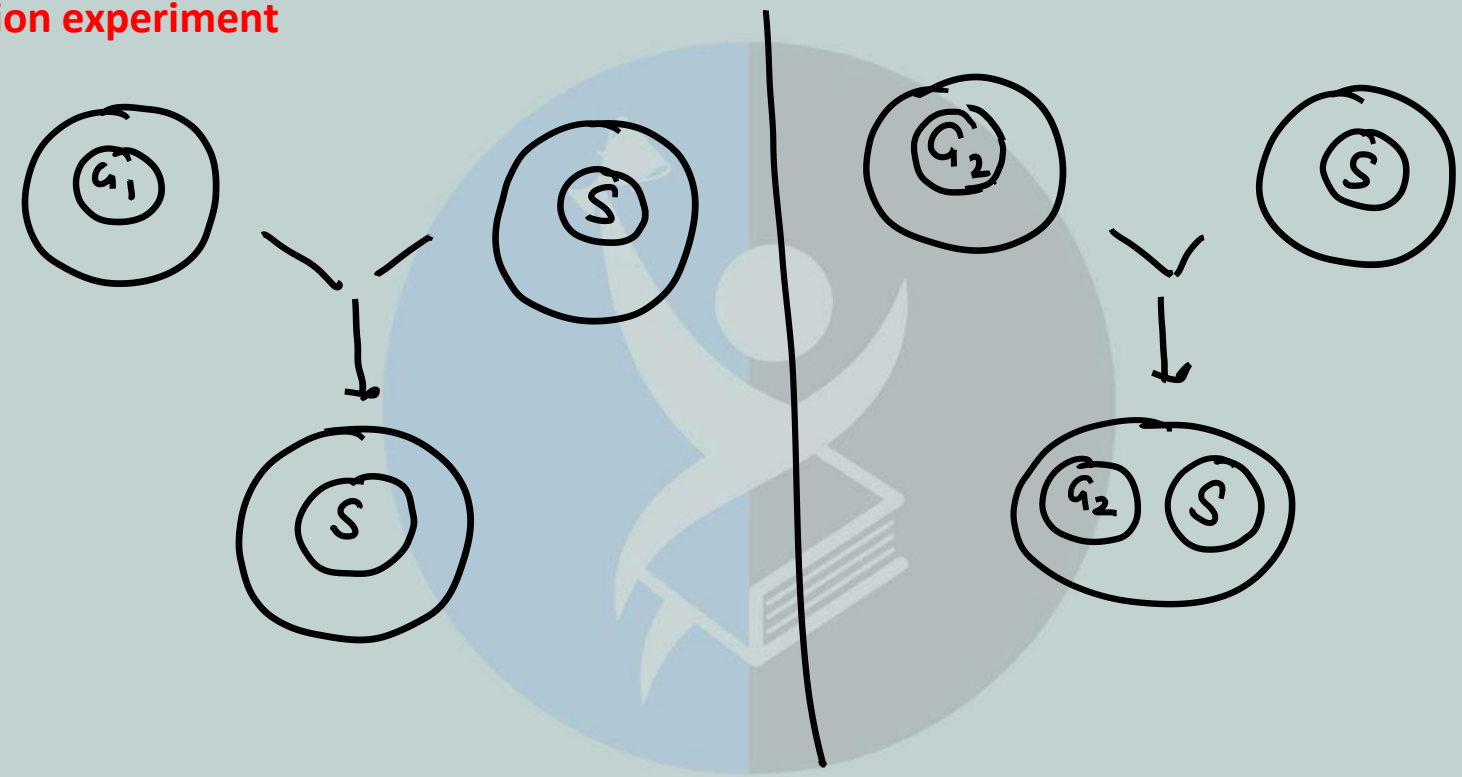
CMG complex formed Replication start → Early S-phase

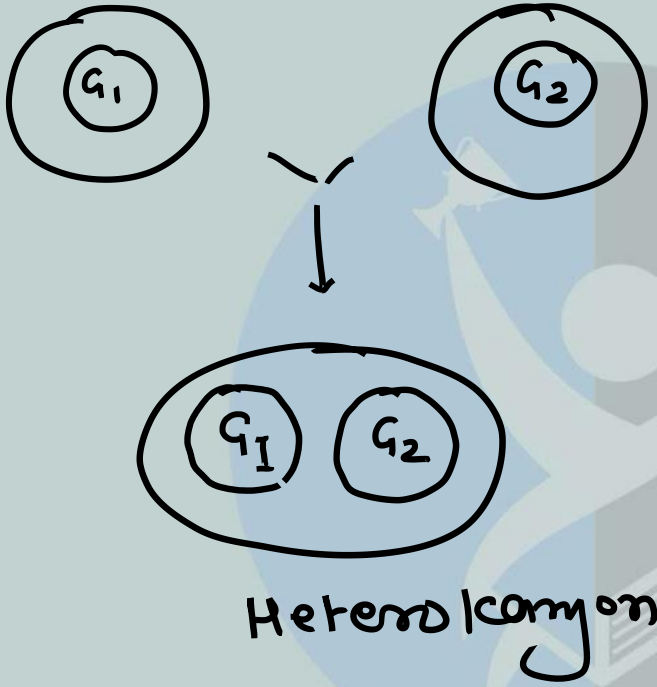
In eukaryotes multiple round of replication is not possible

Reason Once replication is start

- Licensing factor is degraded (Licensing factor is required to load helicase)
- Licensing factor expressed in next G1

Cell fusion experiment

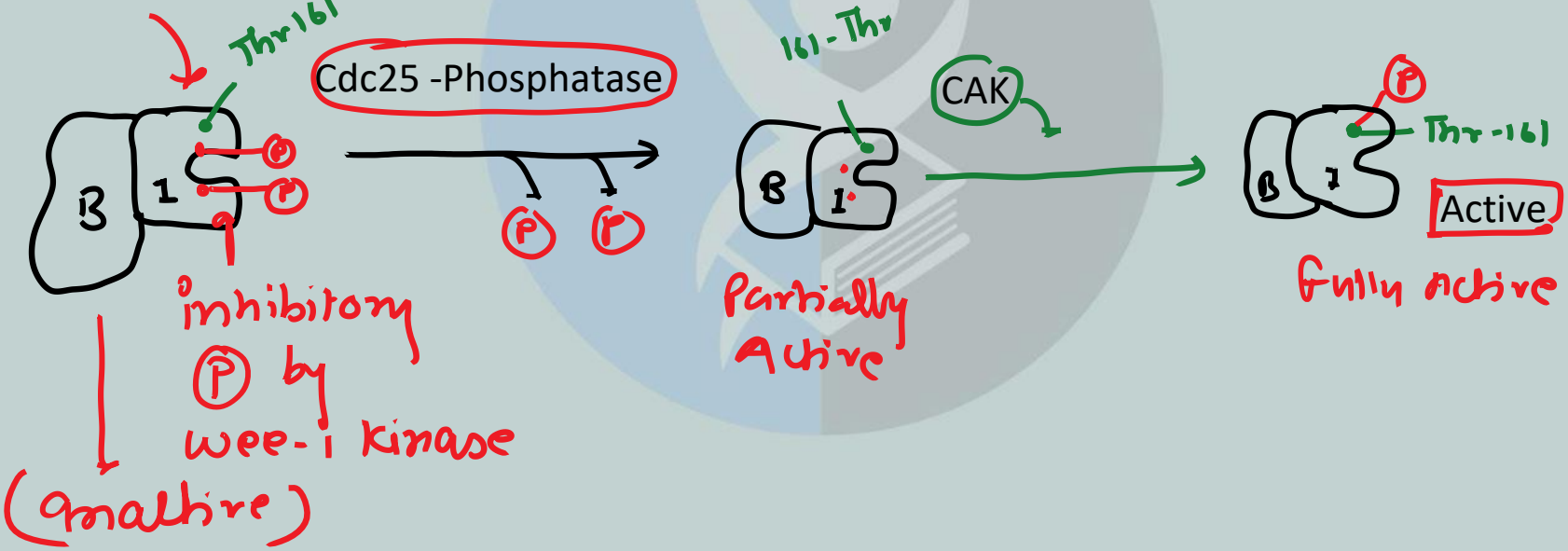



G1
G2
G1
G2
Heterokaryon

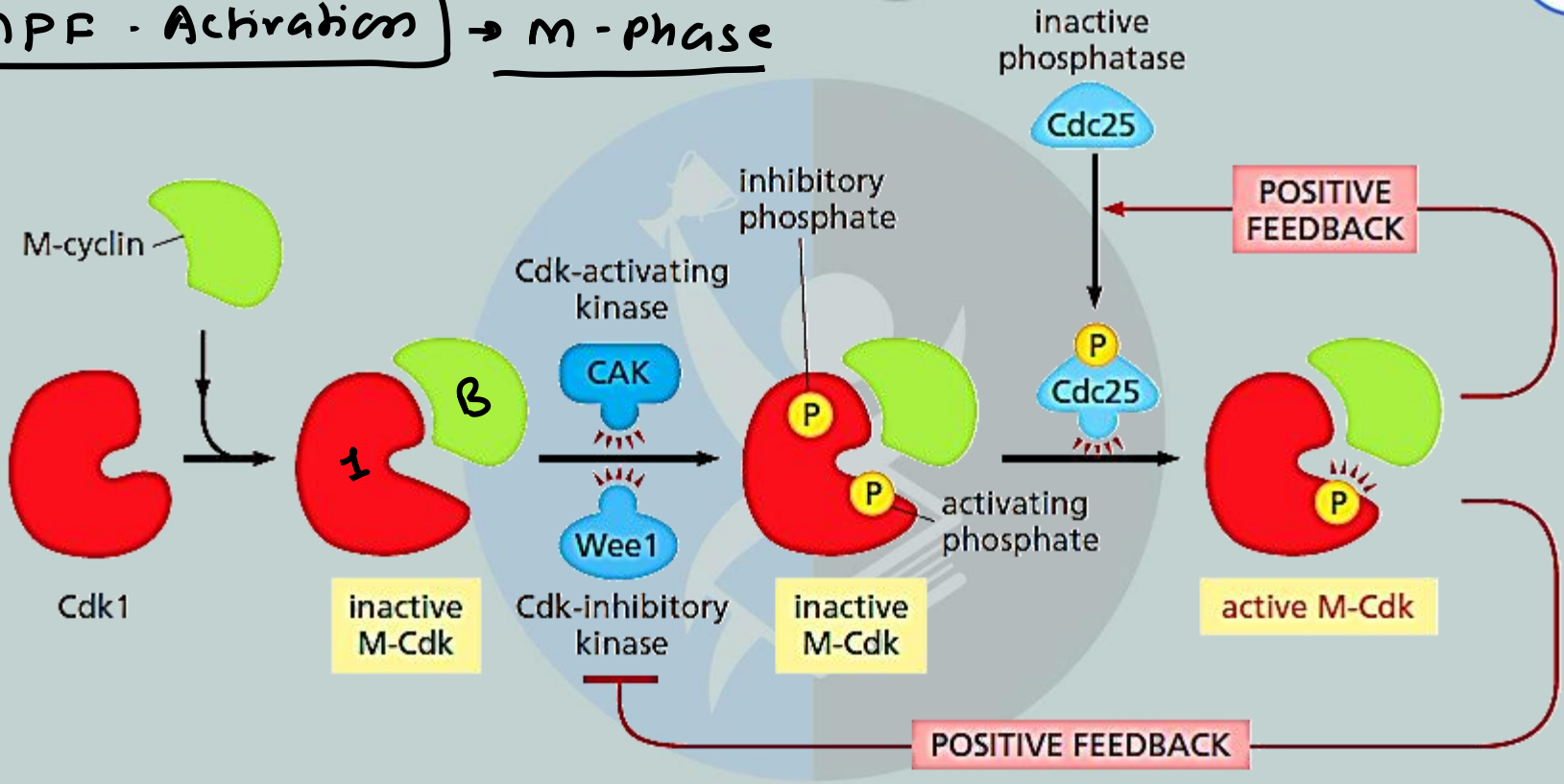
M phase → Cyclin B - Synthesized in mid S - phase

CDK1+Cyclin B -MPF (Mitosis promoting factor)

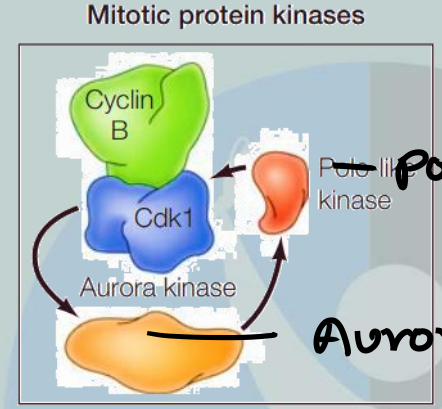
(Inactive)



MPF - Activation → M-phase



MPF

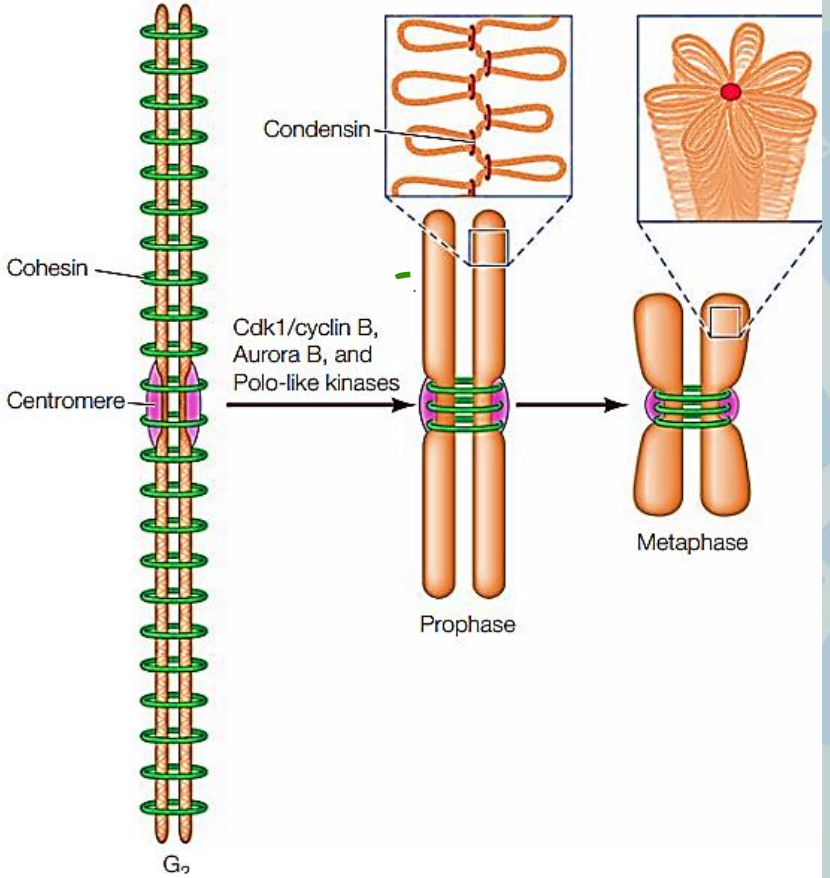


Polo like kinase

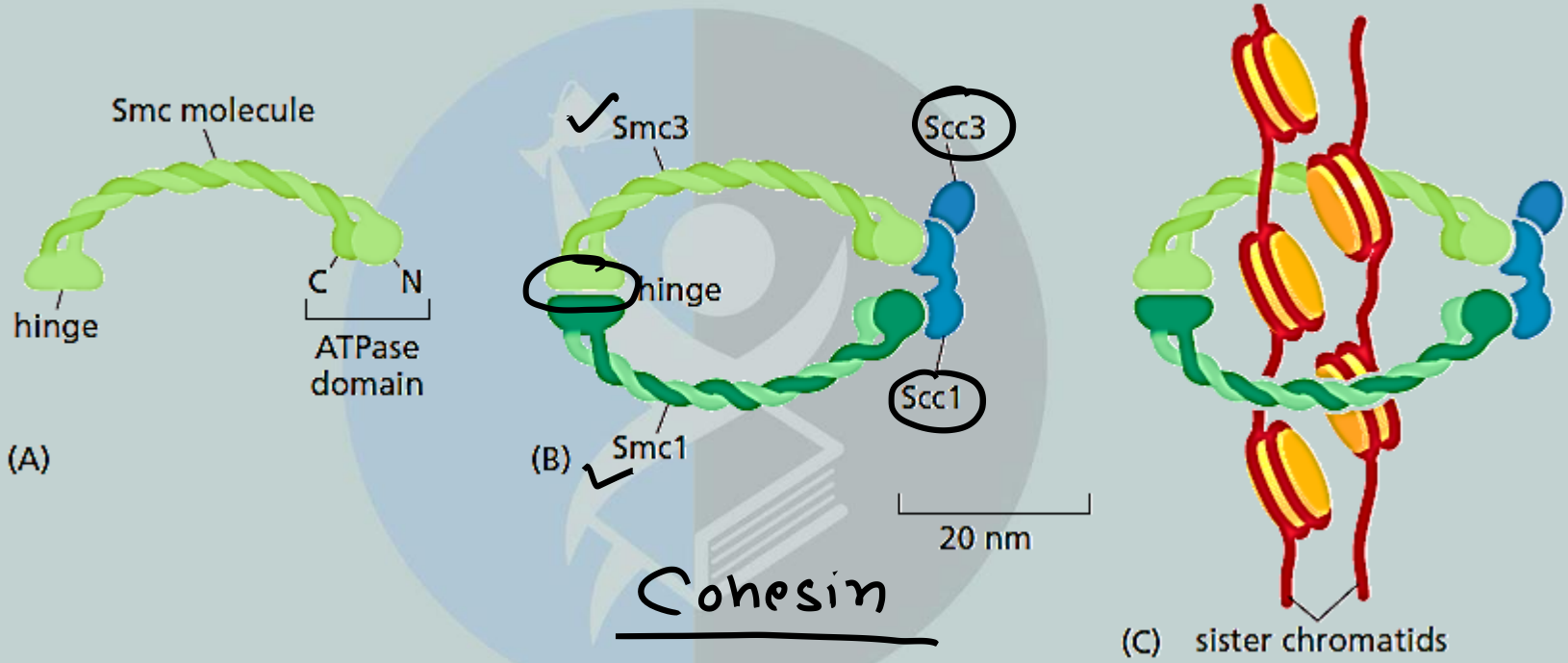
Aurora kinase

Chromatin condensation	Nuclear envelope breakdown	Fragmentation of Golgi apparatus	Spindle formation
Phosphorylation of condensins and cohesins	Phosphorylation of lamins, nuclear pore complexes, and inner nuclear membrane proteins	Phosphorylation of Golgi matrix proteins	Phosphorylation of centrosome, kinetochore, and microtubule-associated proteins

- M-phase Start.



- **The action of cohesins and condensins** Cohesins bind to DNA during S phase and maintain the linkage between sister chromatids following DNA replication
- . As the cell enters M phase, the condensins are phosphorylated by Aurora B kinase and Cdk1, the cohesins by Aurora B and Polo-like kinases.
- The cohesins are replaced by condensins along most of the chromosome, remaining only at the centromere.


Smc molecule
hinge
C
N
ATPase domain
(A)
Smc3
Scc3
hinge
Scc1
(B)
Smc1
20 nm
Cohesin
(C) sister chromatids

General name	Functions and comments
Protein kinases and protein phosphatases that modify Cdks	
Cdk-activating kinase (CAK)	Phosphorylates an activating site in Cdks
Wee1 kinase	Phosphorylates inhibitory sites in Cdks; primarily involved in suppressing Cdk1 activity before mitosis
Cdc25 phosphatase	Removes inhibitory phosphates from Cdks; three family members (Cdc25A, B, C) in mammals; primarily involved in controlling Cdk1 activation at the onset of mitosis
Cdk inhibitor proteins (CKIs)	
Sic1 (budding yeast)	Suppresses Cdk1 activity in G_1; phosphorylation by Cdk1 at the end of G_1 triggers its destruction
p27 (mammals)	Suppresses G_1/S-Cdk and S-Cdk activities in G_1; helps cells withdraw from cell cycle when they terminally differentiate; phosphorylation by Cdk2 triggers its ubiquitylation by SCF
p21 (mammals)	Suppresses G_1/S-Cdk and S-Cdk activities following DNA damage
p16 (mammals)	Suppresses G_1-Cdk activity in G_1; frequently inactivated in cancer

Ubiquitin ligases and their activators	
APC/C	Catalyzes ubiquitylation of regulatory proteins involved primarily in exit from mitosis, including securin and S- and M-cyclins; regulated by association with activating subunits Cdc20 or Cdh1
Cdc20	APC/C-activating subunit in all cells; triggers initial activation of APC/C at metaphase-to-anaphase transition; stimulated by M-Cdk activity
Cdh1	APC/C-activating subunit that maintains APC/C activity after anaphase and throughout G_1; inhibited by Cdk activity
SCF	Catalyzes ubiquitylation of regulatory proteins involved in G_1 control, including some CKIs (Sic1 in budding yeast, p27 in mammals); phosphorylation of target protein usually required for this activity

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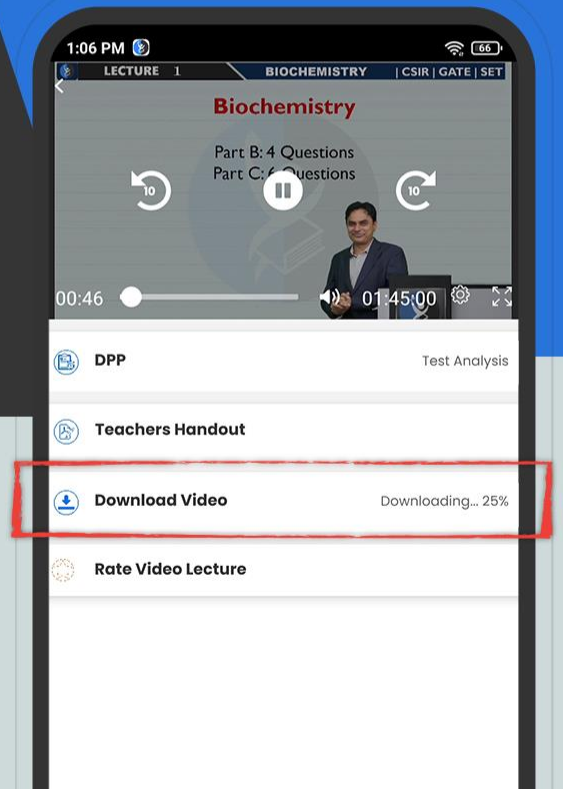

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